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# Pedigree Analysis in Families With Febrile Seizures

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**Febrile seizures are the most common form of seizures, occurring in an estimated 2–5% of North American children. We carried out a systematic pedigree study of febrile seizure probands. Forty of 52 probands (77%) in a referral population selected for increased severity had more than one case per family: one family had 10 cases, one family had 7, 3 families had 6, 2 had 5, 3 had 4, 13 had 3, and 17 had 2 cases.**

**Mode of inheritance in the multicase families best fit the hypothesis of autosomal dominance with reduced penetrance. Polygenic inheritance could not be excluded for some of the smaller families. There was no support for X-linked or mitochondrial inheritance.**

**Penetrance was calculated to be 0.64. Because the cases were selected for increased severity, this represents a useful estimate of the upper limit of penetrance and is in agreement with twin studies.**

**Simulated lod scores showed adequate power for a linkage study in the absence of heterogeneity. Individual families had simulated average lod scores as high as 2.1. However, with potential heterogeneity, assuming only 70% of families share the same disease locus, average lod scores were marginal, and a high density map of marker loci and additional families would be required to document linkage.** © 1996 Wiley-Liss, Inc.

**KEY WORDS: febrile seizures, febrile convulsions, epilepsy, pedigrees, penetrance, autosomal dominant inheritance, reduced penetrance, multifactorial inheritance, SIMLINK, linkage mapping**

## INTRODUCTION

Febrile seizures are the most common form of seizures, occurring in an estimated 2–5% of North American children [Hauser and Kurland, 1975; Leviton and Cowan, 1982; Verity et al., 1985; Forsgren et al., 1990]. Febrile seizures have been defined by various criteria [Consensus Development Panel, 1980; Berg et al., 1992]. The core of the condition involves infants and children who have a convulsion associated with a significant fever and for whom no other cause of the convulsion can be found, such as intracranial infection, metabolic disturbance, or other nervous system abnormality.

Relatives of febrile seizure probands have a higher risk of having a febrile seizure than the general population [Van den Berg, 1974; Tsuboi, 1977; Nelson and Ellenberg, 1978; Fukuyama et al., 1979; Hauser et al., 1985; Verity et al., 1985]. Four twin studies of febrile seizures [Lennox-Buchtal, 1971, 1973; Schiottz-Christensen, 1972; Corey et al., 1991; Tsuboi, 1989] further supported a genetic contribution to the cause.

Complex segregation analysis of 467 nuclear families ascertained through febrile-convulsion probands [Rich et al., 1987] best supported a pure polygenic (or common familial environment) model with a large heritable component (68 ± 7%). The polygenic model was strongly confirmed in families of probands with a single febrile convulsion. In families of probands with repeated episodes of febrile convulsions, the best model was the single-major-locus model with nearly dominant seizure susceptibility [Rich et al., 1987]. Although this study analyzed kindreds, pedigrees were not presented.

Despite the abundance of epidemiological reports [Camfield et al., 1994; Leviton and Cowan, 1982; Frantzen et al., 1970; Van den Berg, 1974; Verity et al., 1985; Fukuyama et al., 1979; Al-Eissa et al., 1992; Berg, 1992; Hauser et al., 1985; Nelson and Ellenberg, 1976, 1983; Forsgren et al., 1990] and the high frequency of the disorder, very few febrile seizure pedigrees have been published, and there has been no systematic study of febrile seizure pedigrees. Only one report, presented in an abstract [Anderson et al., 1988], specifically collected febrile seizure kindreds; four 3-generation families containing 14 affected individuals were mentioned, but pedigrees were not presented. Two studies [Malafosse et al., 1992; Ronen et al., 1993] of

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benign familial neonatal convulsions (BFNC) noted that some individuals in BFNC pedigrees were affected with febrile seizures [Malafosse et al., 1992]. One additional report [Naglo et al., 1987] presented nuclear pedigrees of 11 families in connection with a negative HLA typing study.

The present study is, to our knowledge, the first to present and analyze a large number of systematically obtained febrile seizure pedigrees. The genetic aspects of febrile seizures, such as mode of inheritance and penetrance, need to be better understood before undertaking studies to locate and clone one or more febrile seizure genes. Preliminary reports of this study have appeared [Kugler et al., 1994, 1995].

## MATERIALS AND METHODS

### Ascertainment of the Families

The patients were ascertained retrospectively from a computer printout of all children seen by the Child Neurology Division of the Robert Wood Johnson Medical School between January 1986 and July 1994 with the diagnosis of febrile seizures. A total of 112 families was ascertained. No family was ascertained through more than one patient. Attempts were made to contact these 112 families to verify the clinical and family history. Chart review was carried out to determine if the propositus met the criteria for febrile seizures. However, successful chart review was not sufficient for inclusion in the study. A detailed family history carried out by a trained interviewer, usually by telephone, was required to validate the clinical and family history. An average of one to two informants per family was interviewed, although these informants often contacted other branches of the family for additional information. One of the informants was usually the propositus' mother. Sixty of the 112 families ascertained were not studied further for one of the following reasons: The family could not be contacted despite repeated attempts (26 families); the family did not have sufficient information (15 families); the patient was an adopted child (3 families); or did not meet the criteria for febrile seizures upon subsequent review (16 families). Of these 60 families not studied further, 21 were reported to have multiple cases of febrile seizures in the family, 17 were reported to have only one case of febrile seizures in the family, and for 22 the number of cases was uncertain.

In the present study, inclusion criteria for propositi were at least one convulsion between ages 6 months and 5 years, associated with a recorded temperature of at least 101°F in the absence of a documented intracranial infection or other definable cause. Most temperatures were actually recorded in degrees Fahrenheit by the caregiver, the emergency room, or both; therefore 101°F, slightly more stringent than the more usual 38°C, was used as the threshold for this study. Children whose first seizure was nonfebrile were excluded. Criteria for secondary cases, i.e., additional cases in the family of a proband, were at least one convulsion associated with a report of fever in the absence of epilepsy, a documented intracranial infection, or other definable cause.

Febrile seizure type was further classified as simple vs. complex according to the terminology of the National Collaborative Perinatal Project [NCPP; Nelson, Ellenberg, 1978, 1983]. Complex features included duration (>15 minutes), multiple febrile seizures (>1 per 24 hours), and focality. Recurrent febrile seizures in this study were defined as those occurring more than 24 hours after the initial febrile seizure whether or not during the same febrile illness. In another study, the term recurrent was reserved for seizures occurring only in a later febrile illness [Berg et al., 1992]. In the study of Rich et al. [1987], patients with "multiple febrile seizures" were those with more than one febrile convulsion. To avoid confusion, we used the term "repeated febrile seizures" to mean more than one febrile seizure. Therefore, in this study, probands with repeated febrile seizures were those with multiple febrile seizures plus those with recurrent febrile seizures.

Fifty-two probands remained who had febrile seizures. Detailed pedigrees were taken from these families, extending both the paternal and maternal branches as far as possible.

This study was approved by the Institutional Review Board of the UMDNJ-Robert Wood Johnson Medical School.

### Determination of Penetrance

Pedigrees with multiple affected individuals were analyzed as previously described [Chatkupt et al., 1992; Johnson et al., 1995]. Briefly, each pedigree was divided into one or more sibships of children at risk, defined as the children of a presumed gene carrier. In constructing the sibships of each pedigree it was assumed that individuals in families with 2 or more cases of febrile seizures had a hereditary form of the trait and that that none of the affected individuals in the family represented phenocopies. Since analysis of the pedigrees best supported the autosomal dominant inheritance pattern, the pedigrees were analyzed as though a single dominant gene segregated in the family.

These sibship types (Fig. 1) define the various ways in which an individual (Fig. 1, arrow) may be presumed to be a gene carrier using the assumptions mentioned earlier.

1. Type A: Individual is affected; both anterior and posterior affected relatives occur in the pedigree.
2. Type B: Individual is affected; only anterior affected relatives occur in the pedigree.
3. Type C: Individual is affected; only posterior affected relatives occur in the pedigree.
4. Type D: Individual is unaffected; both anterior and posterior affected relatives occur in the pedigree.
5. Type E: Unaffected couple has only posterior affected relatives in at least 2 separate lines of descent; one individual in the couple is a gene carrier, but it cannot be determined which one.
6. Type F: Unaffected individual without anterior affected relatives produces affected descendents through different unions.

Bilineal sibships were those in which a child was at risk of inheriting the abnormal allele from both parents, from one parent and an anterior relative of the

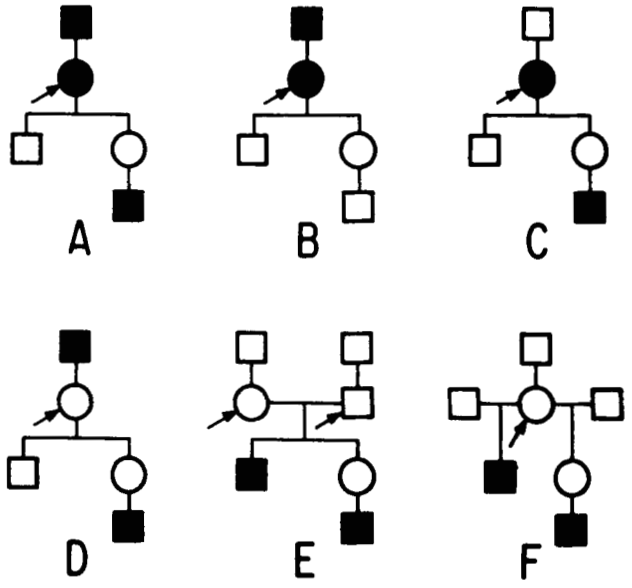


Fig. 1. Six sibship types which allow identification of a parent (arrow) and a gene carrier under the assumptions described in the text. In sibship type E, one parent is a gene carrier, but it cannot be determined which one.

other, or from anterior relatives of both parents. In addition, unless both parents were gene carriers (i.e., affected), at least one posterior relative of the parents was also affected.

An individual was counted only once as a child at risk but could be a gene-carrier parent in one sibship and a child at risk in another.

A database (Paradox 4.5) was used to count the individuals in the various categories. Each record was an individual child of a gene-carrier parent. The database fields included: 1) family name, 2) number of affected individuals in the family, 3) number of the sibship in the family, 4) sibship size, 5) sibship type (A-F, or bilineal sibship), 6) child at risk's phenotype (affected/unaffected), 7) child at risk's sex (male/female), 8) child at risk's status (living/dead), 9) sex of gene-carrier parent (male/female/unknown, i.e., for type E sibships), 10) phenotype of gene-carrier parent (affected/unaffected).

Penetrance was defined here as the probability of the abnormal phenotype given the abnormal genotype. Penetrance was calculated as the observed number of affected individuals (after excluding probands) divided by the number of individuals with the abnormal genotype. The number of individuals with the abnormal genotype was estimated according to the expectations of autosomal dominant inheritance. For all sibship types, except the bilineal sibships, the number of individuals with the abnormal genotype was half of the children at risk (after excluding probands). For bilineal sibships, the probability, $P$, that a child at risk would inherit the abnormal allele was calculated according to the formula:

$$P = [(2^n - 1)(0.5) + 0.75]/2^n$$

where n was the number of generations above the parent for the more distant gene carrier of the 2 lines placing the child at risk. Thus, the probability that the child at risk would be a gene carrier varied between 0.75 when both parents were affected (n = 0) to 0.5 when the nearest gene carrier from one or both lines was a distant ancestor of a parent (n was large).

### Power Studies Using SIMLINK 4.1

The power of these pedigrees for a linkage study was determined using the computer simulation program SIMLINK 4.1 [Boehnke, 1986; Ploughman and Boehnke, 1989]. This program determines the average and maximum lod scores likely to be encountered in linkage studies with a given set of families and markers.

We carried out 2 kinds of simulations. In the first analysis, penetrance was the observed penetrance (0.64, as calculated later). In the second analysis, an affecteds-only analysis, penetrance was set to 0.001 so that the only phenotype information came from affected individuals. In both analyses, a microsatellite marker was simulated. The following parameters were used: 4-allele marker with allele frequencies 0.25, 0.25, 0.25, 0.25; disease allele frequency 0.015 (half the population frequency, 3%, for febrile seizures) with the autosomal dominant model; phenocopy rate = 0.0075; true recombination fractions (theta) 0.0 and 0.10; 1,000 replicates; and locus homogeneity (alpha = 1) or heterogeneity (alpha = 0.7). If alpha = 1, there is locus homogeneity. That is, there is a single disease locus for all families in the dataset. If alpha < 1, there is locus heterogeneity. That is, at least 2 disease loci are represented among families in the dataset. If alpha = 0.7, then 70% of families have the same disease locus, while for the other 30% the disease is unlinked to that locus.

Observed vs. expected values were compared using the chi-square test [Fisher and Yates, 1963]. The Yates correction for continuity was uniformly applied [Fisher and Yates, 1963; Fisher, 1950], and the exact treatment of 2 × 2 tables was used when appropriate [Fisher, 1950].

## RESULTS

### Characteristics of the Febrile Seizure Probands

There were 52 probands who had at least one febrile seizure. Of these, 40 (77%) had at least one additional case of febrile seizure in the family. The mean age of the first febrile seizure was 16.5 months (range 6–55 months) among multicase probands and 19.8 months (range 6–48 months) among single-case probands.

The probands were classified (Table I) according to whether the febrile seizures were simple or complex [Nelson and Ellenberg, 1976, 1978, 1983]. For one proband, there was insufficient clinical information to determine whether the febrile seizures were simple or complex. There was a higher proportion of complex febrile seizures (50%) among multicase probands than among single-case probands (25%), but the difference was not significant.

In 45% of probands for whom information was available (n = 51) febrile seizures were complex, while in only 19.7% of probands from a population-based study

TABLE I. Complex Febrile Seizures in Single and Multicase Probands*

| | Multicase probands (n = 40) | Single case probands (n = 12) |
|---|---|---|
| Simple | 19 (17) | 9 (8) |
| Complex | 20 (15) | 3 (2) |
| Duration[a] | 5 (4) | 1 (0) |
| Multiple[b] | 12 (8) | 2 (2) |
| Focality[c] | 3 (3) | 0 (0) |
| Simple/complex unknown | 1 | 0 |
| Recurrent or multiple | 36 | 10 |

*Numbers in parentheses are those with recurrent febrile seizures, i.e., those with a second febrile seizure occurring more than 24 hours after the first febrile seizure.
[a]Greater than 15 minutes.
[b]More than one per 24 hours.
[c]Focal onset or Todd's paralysis.

[Verity et al., 1985] were febrile seizures complex. This difference was statistically significant ($\chi^2 = 20.797$, df = 1, $P < .001$).

Of multicase probands, 36 had more than one febrile convulsion (multiple or recurrent febrile seizures). Almost all of these recurrent episodes occurred during different febrile illnesses. Three multicase probands had only a single febrile seizure; one of these was complex, based upon protracted duration, and 2 were simple. For one proband, there was insufficient information to determine whether or not the febrile seizure(s) were single.

### Analysis of the Febrile Seizure Pedigrees

Since Rich et al. [1987] found different inheritance patterns in their patients depending upon whether probands had a single or repeated febrile seizures, we compared our group of multicase probands with their multifactorial subgroup and with their "nearly dominant" subgroup with respect to single or repeated febrile seizures in the probands. The present group of multicase probands, in which 3 of 39 probands (7.7%) had only a single febrile seizure, was not significantly different ($P = 0.5622$ by exact calculation of $2 \times 2$ table [Fisher, 1950]) from the single major locus group of Rich et al. [1987], in which one of 21 probands (4.8%) had only a single febrile seizure, but was significantly different ($\chi^2 = 18.518$, df = 1, $P < .001$) from their polygenic group, in which 28 of 53 probands (53%) in the polygenic category had only a single febrile seizure. This suggested that inheritance pattern in the the present multicase families was better characterized as dominant than multifactorial.

Of the 40 multicase probands, 27 were males and 13 were females ($\chi^2 = 4.900$, df = 1, $P < .10$ [not significant, ns]). For the secondary cases, there were 51 males and 39 females ($\chi^2 = 1.600$, df = 1, $P < .30$ [ns]). Among the 12 single-case probands, 6 were males and 6 were females (ns). After exclusion of probands, there were 11 instances of male-to-male transmission, 5 of male-to-female transmission, 14 of female-to-male transmission, and 9 of female-to-female transmission (ns). The equal sex ratio among probands and secondary cases and the transmission pattern with numerous examples of male-to-male transmission supported the hypothesis that transmission of febrile seizures was autosomal as well as dominant in this group of families.

Of the 40 multicase pedigrees, one family had 10 affecteds, one family had 7, 3 had 6, 2 had 5, 3 had 4, 13 had 3, and 17 had 2 affected pedigree members. Among the 17 families with only 2 affected individuals, there were 10 parent-child pairs, 3 aunt/uncle-niece/nephew pairs, 2 sib pairs, one first cousin pair, and one half-sib pair. The pedigrees with more than 2 cases of febrile seizures are shown in Figures 2 and 3. The frequent observation of vertical transmission, especially through 3 generations, supported the hypothesis of autosomal dominant transmission for our multicase probands. The observation of transmission through unaffected individuals in some pedigrees suggested that penetrance was reduced. The possibility that this group contained some multifactorial families was not excluded, especially for the smaller families.

Of multicase propositi, 37 had only febrile seizures. Three of these had nonfebrile seizures following recurrent episodes of febrile seizures. The first patient (propositus in pedigree 8, Fig. 2) had a febrile seizure lasting 10 minutes at age 17 months. Two weeks later, he had a febrile seizure lasting 90 minutes. Thereafter he had repeated febrile and nonfebrile generalized convulsions. He had 3 relatives who had only febrile seizures. The second child (propositus in pedigree 9, Fig. 3) had the onset of febrile convulsions at age 18 months and "many" subsequent febrile convulsions, 2 of which may have been nonfebrile or associated with temperatures below 101°F. He had 2 relatives who had only febrile seizures. The third patient (pedigree not shown) had febrile seizures at ages 18 and 27 months. At age 4 years, he had 3 apparently nonfebrile convulsions within a one-month period, each lasting less than one minute, one with focal features. His half brother had a single febrile seizure. These 3 multicase families were included because the febrile seizures preceded the nonfebrile or possibly nonfebrile seizures, and because the other affected family members had exclusively febrile seizures and no family history of epilepsy. No relatives of propositi were found who had only nonfebrile seizures.

Among the single-case propositi, one child had 23 convulsions, all of which were febrile except for 2: During one, the child "felt warm" but did not have the temperature measured; the other was associated with

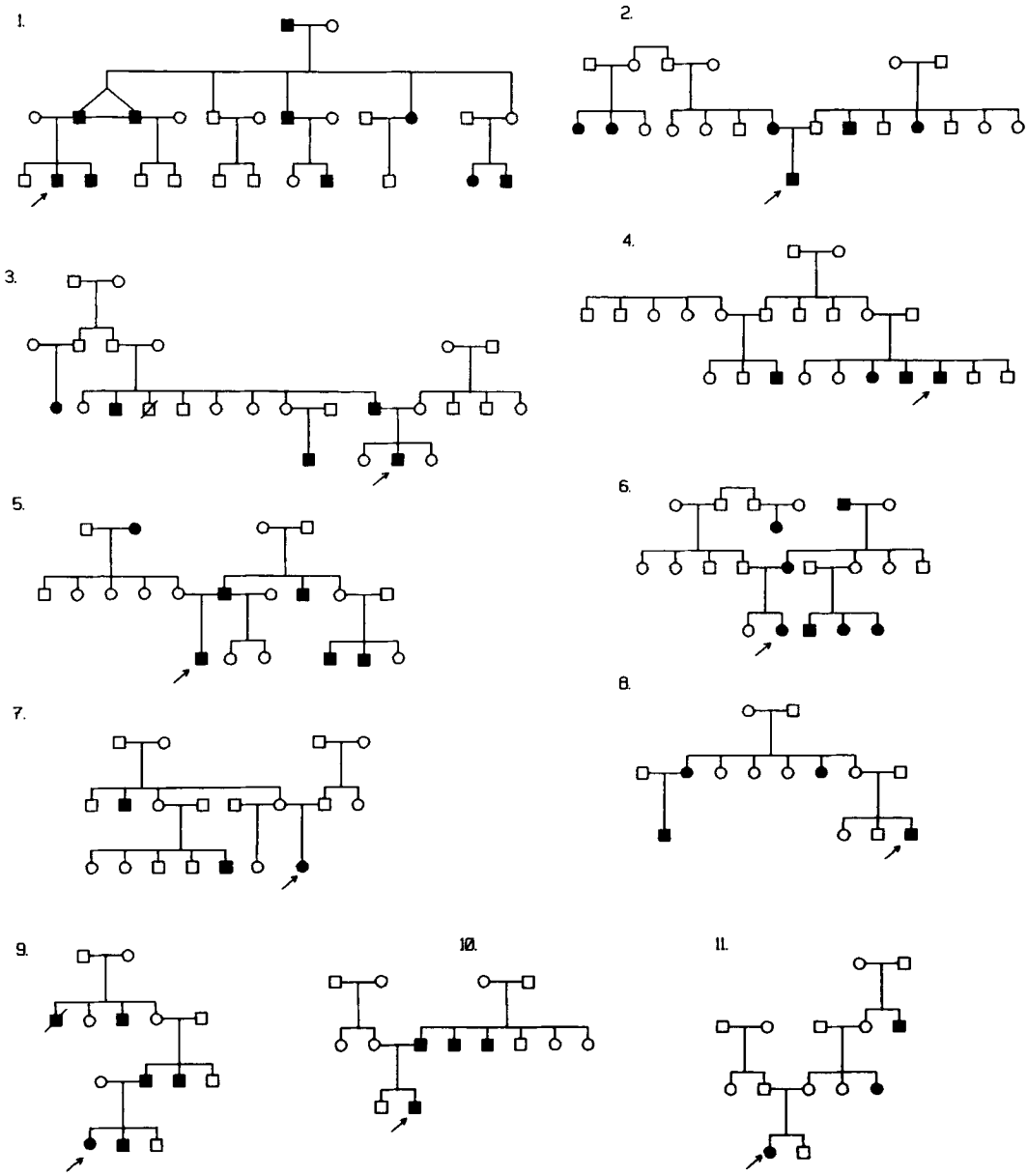


Fig. 2. Eleven febrile seizure kindreds with maximum simulated lod scores greater than 1.0 and mean simulated lod scores greater than 0.5.

meperidine and nitrous oxide anesthesia during dental work.

## Estimation of Penetrance

Before exclusion of propositi in the 40 multicase families, there were 110 affected individuals among 260 offspring at risk. Both parents were affected for only one of the 5 bilineal sibships; in this sibship and 2 of the other bilineal sibships, the propositus was the only child and was thus excluded. In the 2 other bilineal sibships, the risk to 2 children at risk was negligibly different from 0.5, and the value of 0.5 was used. Penetrance was therefore $(110 - 40)/([260 - 40] \times 0.5) = 0.64$.

Penetrance in offspring of male gene carriers was 0.67 and in offspring of female gene carriers was 0.70 (ns).

## Power Studies Using SIMLINK 4.1 Analysis of the Pedigrees

The simulated lod scores for the multicase families are shown in Table II. Among individual families, one had a simulated mean lod score greater than 2.0 (pedigree 1, Fig. 2), 4 had simulated mean lod scores greater than 1.0 (pedigrees 2, 3, 4, and 6, Fig. 2), and 6 had simulated mean lod scores greater than 0.5 (pedigrees 5 and 7–11, Fig. 2). We also carried out power studies for an affecteds-only analysis (Table II) because this ap-

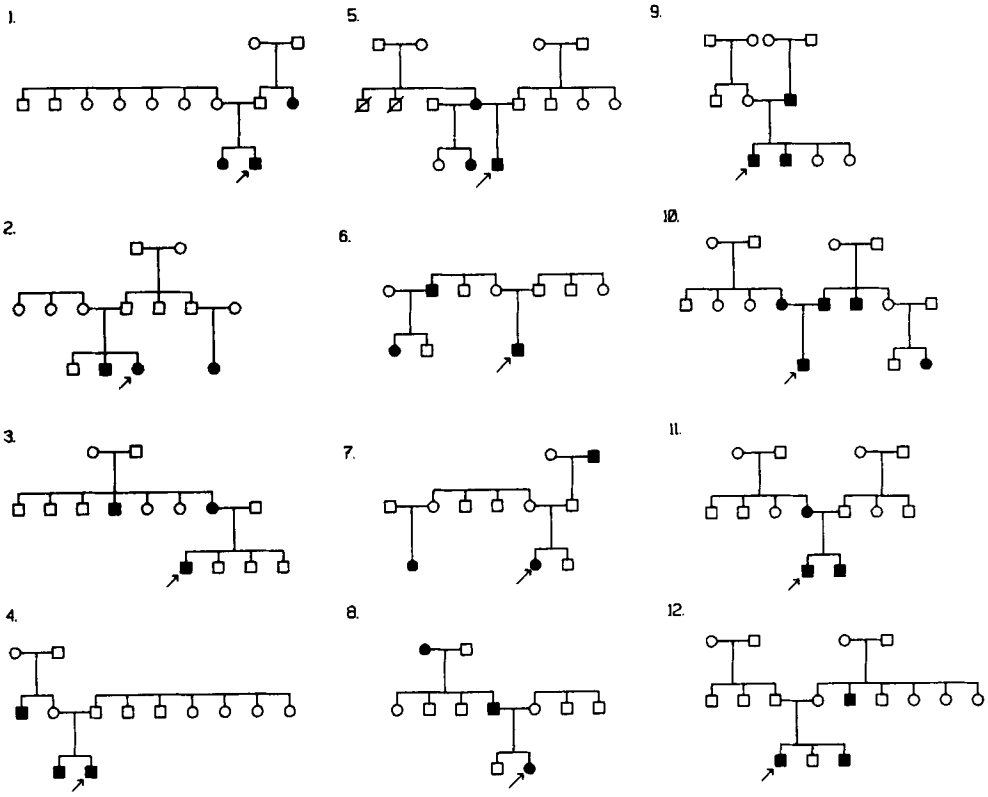


Fig. 3. Additional febrile seizure kindreds with 3 or more affected individuals.

proach minimizes the effects of reduced penetrance though at the expense of some power.

## DISCUSSION

The 52 propositi in the present study were limited to those febrile seizure patients from whose caregivers a rigorous family history could be taken. Family histories from patient charts were not accepted without such verification. Thus, many potential propositi, including at least 20 apparently multicase families, were not included in the present analysis.

Our patients also had a high proportion of multicase families: 77% of families had 2 or more cases. Seven of 40 families had high-density pedigrees with 5 or more cases per family. This large fraction of multicase and high-density families may be accounted for by 2 factors: first, our pedigrees went beyond first and second-degree relatives, and second, because these probands had been referred for pediatric neurological consultation, they were likely to have multiple or recurrent febrile convulsions and therefore to come from dominant rather than polygenic pedigrees. Since a retrospective study such as the present one is subject to recall bias, especially in older pedigree members, the fraction of hereditary cases may be underestimated and may be even higher.

The most likely inheritance pattern for our multicase families was autosomal dominant with reduced penetrance. Polygenic inheritance may occur in few of our smaller families [Rich et al., 1987]. Analysis of the data failed to support X-linked or mitochondrial inheritance.

TABLE II. Simulated Lod Scores in 40 Families*

| | No heterogeneity | | | | With heterogeneity | | | |
|---|---|---|---|---|---|---|---|---|
| | theta = 0.00 | | 0.10 | | 0.00 | | 0.10 | |
| | Mean | Max. | Mean | Max. | Mean | Max. | Mean | Max. |
| Penetrance | | | | | | | | |
| 0.64[a] | 17.1 | 24.6 | 7.0 | 16.5 | 8.1 | 18.5 | 3.6 | 11.3 |
| 0.001[b] | 13.1 | 17.6 | 5.0 | 12.1 | 6.0 | 14.9 | 2.5 | 9.3 |

*Lod score $\geq 3.0$ is comparable to $P \leq 0.001$ and is regarded as evidence of linkage [Morton, 1955].
[a]Observed penetrance.
[b]Affecteds-only analysis.

Penetrance, calculated for the first time for putative febrile seizure genes, was found to be 0.64. This referral population was an excellent one for estimation of the upper limit of penetrance since this group was enriched in autosomal dominant families while population-based studies consist mostly of polygenic cases. This result for penetrance can be compared with monozygotic (MZ) twin concordances which also estimate penetrance. Reported pairwise MZ twin concordances vary between 19–69% among different studies [Schiottz-Christensen, 1972; Lennox-Buchtal, 1973; Corey et al., 1991]. Anderson et al. [1989] suggested that high values of MZ concordance may be biased, in part because of selective bias toward more severe cases. This suggestion is supported by the difference in pairwise MZ twin concordances in Tsuboi's study [Tsuboi and Endo, 1991] between MZ twins from population-based ascertainment (44% concordance) and clinic-based ascertainment (82% concordance) which give a combined concordance of 69%. Since the present population was selected for severity, it is not surprising that the present penetrance compares best with the higher estimates of MZ concordance [Lennox-Buchtal, 1973; Tsuboi and Endo, 1991] which may be similarly biased. However, it is premature to use this estimate of penetrance for genetic counseling both because it is an upper limit and because it requires confirmation.

The number of bilineal sibships (5 of 40 multicase families, 3 of 7 high-density families) also raised the question of polygenic inheritance. However, since febrile seizures occur so commonly in the population (2–5%), bilineal pedigrees would be expected to occur.

Three of the multicase probands developed nonfebrile or possibly nonfebrile seizures following multiple episodes of febrile seizures. Reportedly, 2–13% of patients with febrile seizures go on to have nonfebrile seizures depending upon the number of risk factors [Nelson and Ellenberg, 1983]. Mesial temporal sclerosis occurs in some patients with complex or repeated febrile seizures [Falconer et al., 1964; Cendes et al., 1993], but it is not clear whether this results from or causes the febrile seizures. The fact that the febrile seizure propositi who later developed nonfebrile seizures occurred in families with up to 4 cases of febrile seizures suggests that they represent true genetic cases of febrile seizures.

This referral population from a child neurology service represents a suitable one for studies directed toward locating and cloning one or more febrile seizure genes since it is enriched in autosomal dominant pedigrees. Simulated lod scores (Table II) showed that the 40 multicase families had adequate power for linkage analysis in the absence of heterogeneity. Individual families had simulated mean lod scores as high as 2.1. However, if heterogeneity was present with only 70% of families sharing the same disease gene locus, average lod scores were marginal, and a high-density map of marker loci and additional families could be required to document linkage. If a high degree of heterogeneity is encountered, methodology used for genetically complex diseases may be required to detect linkage, such as that described for diabetes genes [Thomson, 1994].

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